REMARKS

Claims 1-6, 9 and 12-19 are pending in the above-referenced patent application and are currently under examination. Claims 9, 12, 13, 15 and 19 have been amended. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

In the Office Action, claims 1-6, 13, 14 and 16-19 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. In addition, claims 1-8 ([sic] claims 9 and 15) have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. For the reasons set forth below, each of these rejections is overcome.

Rejection Under 35 U.S.C. § 112, First Paragraph

In the Office Action, claims 1-6, 13, 14 and 16-19 have been rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is allegedly not enabling for methods in which either of the constructs is not integrated into the genome and is allegedly not enabling for the production of an organism other than a mouse. It is our understanding that the latter portion of this rejection applies to claim 19, which, prior to the present Amendment, was directed to the production of transgenic mice and pigs. In order to expedite prosecution, and without prejudice or disclaimer, Applicants have amended claim 19 to delete reference to pigs and porcine cells.

With respect to the remainder of this rejection, the Examiner is respectfully requested to reconsider this rejection in view of the following remarks. As an initial matter, it is unclear why claims 13 and 14 have been included in this rejection. A perusal of claims 13 and 14 reveals that these claims are dependent from claim 12, which recites both constructs as being for genomic integration. Moreover, claim 19, as amended, recites that the first construct is integrated. As such, it is Applicants' understanding that this rejection does not apply to claims 12-14 and 19.

With respect to the other claims, the Examiner indicates that the specification is not enabling for a method in which either of the constructs is not integrated into the genome of the cell. However, the specification makes it clear that the second construct is to be integrated into the genome because it is the "trap" vector, and the claims recite the limitation of integration of the second construct. Moreover, it is respectfully pointed out that one of skill in the art would appreciate that the first construct (which comprises the promoter having restricted expression) need only be capable of expression in the cell so that its product can interact with the trapped vector or a

product encoded by the trap vector. Integration of the first construct is ***not*** essential. The Examiner appears to be concerned that the specification does not teach constructs that are self-replicating.

Applicants respectfully submit that such claims directed to the use of self-replicating constructs are fully enabled by the specification as filed and, thus, such claims do not need to be amended for the following reasons. More particularly, it is respectfully submitted that as of the filing date of the present application, it was routine for a person of skill in this field to make and use self-replicating expression vectors without undue experimentation. Expression vectors that replicate as episomes in mammalian cells were routinely used. In support of this position, Applicants provide the Examiner with a copy of page 11.69 of "Molecular Cloning – A Laboratory Manual" (3d) Sambrook, J. and Russell, D. W. Although the latter reference was published in 2001, it describes how expression vectors that replicate as episomes in mammalian cells were known and described in references dating from 1986. Moreover, Applicants provide the Examiner with a copy of pages 696-7 of "Guide to Molecular Cloning Techniques" in *Methods in Enzymology* (1987) Vol. 152, which demonstrates that as of 1987, various episomal viral vectors were known for expression and stable maintenance in cells. In addition, Applicants provide the Examiner with a copy of an abstract of a publication by Margolskee, R. F. *et al* (1988) *Mol. Cell Biol. 8*:2837-47, which describes the use of an episomal viral vector (based on Epstein-Barr virus) for expression and stable maintenance in human cells (in this case, hematopoetic cells). The latter reference is only an example of what the literature provided as of the filing date of the present patent application. Clearly, the specification, coupled with the general knowledge in the art, provides more than sufficient guidance to allow one of ordinary skill in the art to make and use self-replicating vectors.

In view of the foregoing, Applicants respectfully submit that the pending claims are fully enabled by the specification as originally filed, either alone or together with the general knowledge in the art available as of the filing date of the present patent application. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. From a review of the Office Action and pending claims, it appears that this rejection is directed to claims 9 and 15.

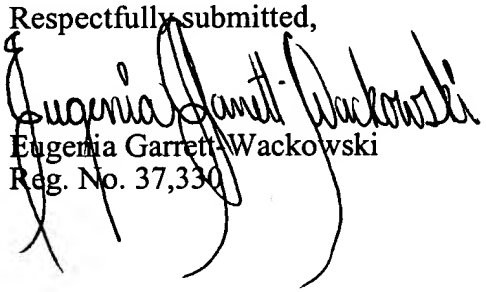
In order to expedite prosecution, claims 9 and 15 have been amended in accordance with the Examiner's suggestion. As such, the Examiner's concern has been overcome. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims

Claims 9, 12, 15 and 19 have been amended as follows:

9. (Amended) A DNA construct comprising, in a 5' to 3' direction, a splice acceptor, a sequence encoding an inactive subunit or fragment of an enzyme and, an IRES wherein said sequence encoding the enzyme subunit or fragment is not operably linked to a transcription control element, and wherein said subunit or fragment is active when combined with a further subunit [or fragment of an enzyme].

12. (Amended) The combination of:

(i) a DNA construct for integration into the genome of an eukaryotic cell comprising a sequence encoding a first indicator component under the control of a promoter having restricted expression; and

(ii) a DNA construct for integration into the genome of a eukaryotic cell, comprising in the 5' to 3' direction, a splice acceptor, a sequence encoding a second indicator component not operably linked to a transcription control element, and an optional IRES, wherein expression of both the first and second indicator components in said cell is detectable.

13. (Amended) A [eucaryotic] eukaryotic cell[s] transformed by the combination of DNA constructs of claim 12.

15. (Amended) A DNA construct comprising, in a 5' to 3' direction, a splice acceptor and a sequence encoding an inactive alpha or omega fragment of β-galactosidase, wherein said sequence encoding the inactive alpha or omega fragment is not operably linked to a transcription control element and said fragment is active when combined with another fragment of β-galactosidase.

19. (Amended) A method of producing a mouse [or a pig] comprising a detectable indicator associated with a target gene having restricted expression, which comprises:

(i) transforming a murine [or porcine] ES cell [with] by integrating into the cell's genome, a first DNA construct encoding a first indicator component under the control of a promoter having restricted expression;

(ii) transforming the cell of (i) or a descendent of the cell by integrating into the cell's genome, a second DNA construct comprising DNA encoding a second indicator component not operably linked to a transcription control element;

(iii) selecting transformed cells of (ii);

(iv) introducing selected cells of (iii) into a murine or porcine host embryo;

(v) implanting the host embryo of (iv) into a pseudopregnant mammal;

(vi) maintaining the mammal of (v) while offspring develops to term from the host embryo; and

(vii) selecting offspring of (vi) by the presence of a detectable indicator resulting from both the first and second indicator components in tissue or specialized cells of the offspring.